

**REMARKS**

Claims 1-8, 13, and 16-17 are pending in this application. New claims 18 and 19 are added through the instant Preliminary Amendment.<sup>1</sup>

Claims 1-8, 13, and 16-17 were rejected. The Examiner made the following rejections:

- 1) The Examiner rejects claims 1, 2, 4-8, and 13 under 35 U.S.C. § 103(a), as allegedly unpatentable over Caruso (U.S. Patent 6,043,244) or Plachetka (U.S. Patent 5,872,145). In addition, the Examiner rejects claim 3, under 35 U.S.C. § 103(a), as allegedly unpatentable over Caruso or Plachetka in combination with Azia *et al.* (U.S. Patent 4,758,423) or Plachetka *et al.* (U.S. Patent 6,495,535). Claims 16 and 17 are rejected under U.S.C. § 103(a), as allegedly unpatentable over Peyman (U.S. Patent 5,855,907).

The Applicants' remarks are presented in the same order as the rejections set out above.

**I) The Claims Are Not Obvious**

**A) The Incorporation of Steroids is Not Taught by the Art Previously Cited by the Examiner.**

In the Office Action mailed May 20, 2005, the Examiner recycles (almost verbatim) the rejections previously raised, in the Office Action mailed September 09, 2004, in view of 35 U.S.C. § 103(a). The Applicants note that each of the pending claims recite the administration of a formulation<sup>2</sup> comprising, in part, dihydroergotamine and a steroid. However, the teachings in U.S. patents 6,043,244, 5,872,145, 4,758,423, and 6,495,535 are completely silent regarding the co-formulation of a steroid with any of the anti-migraine therapeutics taught therein or in methods for administering the same.

While the Examiner discusses Caruso, Plachetka, and Azria (alone and in combination) with respect to the alleged disclosure of a pH-adjusting agent in a formulation comprising dihydroergotamine, the Examiner points to nothing in these references that would make the

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<sup>1</sup> Claim 18 omits the limitation of a "pH adjusting agent" (as found in claim 1). Claim 19 creates a closed group, for the formulation, consisting of dihydroergotamine and cortisol.

<sup>2</sup> In a method for treating migraines.

administration of a co-formulation of dihydroergotamine *and a steroid* in methods for the treatment of migraine obvious. Indeed, the Examiner's only hint that another element (i.e. a steroid) need be considered in view of the claimed embodiments of the present invention is given where the Examiner states<sup>3</sup> that "[a]dditional active agents may be added to the composition (Col. 8, lines, 12-27)". Turning to this excerpt from the '244 patent, Caruso teaches that,

". . . in addition to the antimigraine drug and antimigraine- potentiating amount of an NMDA receptor blocker or substance that blocks a major intracellular consequence of NMDA receptor activation, the therapeutic composition herein can contain at least one other pharmacologically active substance e.g., caffeine (a stimulant), an antiemetic drug such as metoclopramide, domperidone, belladonna alkaloids and phenothiazines such as chlorpromazine, prochlorperazine, and promethazine, a non-narcotic analgesic, e.g., acetaminophen or a nonsteroidal anti-inflammatory drug such as aspirin, diclofenac, diflusal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tolmetin, zomepirac, and the like."

This laundry list of "additional active ingredients", however, fails to disclose steroids. The Examiner is reminded that in determining the propriety of the Patent Office case for obviousness, it is necessary to determine whether or not the referenced teachings would appear to be sufficient for one of ordinary skill in the relevant art to make the proposed substitution, combination or other modification in question. Surely it is not the Examiner's position that a list which fails to disclose a claim element, as either a genus or a species, is sufficient to render the same as obvious.

Moreover, two of the art references previously cited by the Examiner teach away from steroid co-formulation to the extent they are completely silent on steroid co-formulations yet provide detailed teachings regarding co-formulation with non-steroidal anti-inflammatories (NSAID's).

Similarly Plachetka teaches that:

"It has now been discovered that a combination therapy of a 5-HT agonist, including drugs structurally similar to 5-HT agonists like sumatriptan or like members of the ergot family of compounds, combined with a long acting

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<sup>3</sup> In view of the '244 patent to Caruso.

*nonsteroidal anti-inflammatory drug (NSAID)* substantially reduces or eliminates the relapse phenomenon in a significant portion of migraineurs that otherwise experience relapse and that the combination of the two agents results in an enhanced therapeutic effect allowing for greater and/or longer lasting efficacy and/or lower doses than can be obtained with the conventional doses of either individual agent." U.S. Patent 5,872,145, Col. 4, ll. 50-60. (emphasis added).

Once again while providing a detailed teaching on the co-formulation of nonsteroidal anti-inflammatory compounds Plachetka, like Caruso, is silent on co-formulating steroids with any of the anti-migraine formulations taught in the '145 patent.

In contrast, as previously noted,<sup>4</sup> the Applicants appreciate that steroids have beneficial therapeutic properties<sup>5</sup> (vis-à-vis the treatment of migraine) and that sublingual administration of steroids allows for a prospective reduction of dose (and, thereby, reduction of side effects and toxicities) given: i) the direct transmucoal delivery into the bloodstream and ii) a reduction of the first pass effect associated with enteral administration. For example glucocorticoid, in part, stimulates gluconeogenesis and inhibits the uptake of glucose from muscle and adipose tissue. These physiological effects would be desirable in supplementing the action of DHE in methods for the treatment of migraine.

The '244 patent to Caruso and the '145 patent to Plachetka would likely lead an investigator in a direction divergent from the path taken by the Applicants. These references provide evidence of the *non-obviousness* of the claimed embodiments of the present invention and, therefore, rebut the very rejections<sup>6</sup> for which there were cited. See, *In re Gurley*, 27 F.3d 551, 553, 31 U.S.P.Q.2D (BNA) 1130, 1131 (Fed. Cir. 1994).

**B. The Teachings in U.S. Patent 5,855,907 to Peyman are of no Moment**

Peyman teaches the co-formulation of "an effective amount of an opioid" with five different categories of drugs: i) vasoconstrictors, ii) antiinflammatories (including steroids), iii) antimicrobials, iv) non-opiate antimigraine drugs, and v) decongestants.<sup>7</sup> As the Examiner notes, Peyman teaches "a method treatment of migraine comprising the topical administration of *an opioid* with combination of anti-inflammatory compounds include (sic.) steroids, particularly

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<sup>4</sup> See, Applicants Preliminary Amendment filed on March 09, 2005.

<sup>5</sup> The Applicant also notes there is no obligation to describe the underlying mechanism of he claimed methods and the following remarks in no way limit the scope of the invention as claimed.

<sup>6</sup> Raised under 35 U.S.C. 103(a).

<sup>7</sup> See, U.S. patent 5,855,907, Cols. 5 and 6.

glucocorticoids, for example, cortisol, cortisone, prednisolone, dexamethasone and the like."<sup>8</sup> (emphasis added). However, Peyman is completely silent on the formula of *dihydroergotamine* with a steroid. Moreover, in the background section, Peyman teaches that:

"[t]here are also specific antimigraine treatments, which include ergotamine and its related compounds, such as sumatriptan and dihydroergotamine, which are agonists of 5-HT(1B) and 5-HT(1D) receptors. Sumatriptan is administered orally, by subcutaneous injection, or as a nasal spray. Dihydroergotamine is administered intramuscularly, or as a nasal spray. These treatments are associated with the risk of coronary vasospasm."

That is to say, Peyman identifies an undesirable side effect (i.e. coronary vasospasm) experienced by some patients with certain types dihydroergotamine administration and uses this teaching as a departure point to discuss the use of *non-dihydroergotamine* containing opioid co-formulations in the treatment of migraine. Therefore, Peyman's: i) advisory regarding the side effect of dihydroergotamine administration and ii) silence on formulating dihydroergotamine with a steroid, renders the '907 patent insufficient to sustain a rejection under 35 U.S.C. 103(a).

**C. Four Years After the Filing of the Application, the Examiner Still Fails to Make a Prima Facie Case for the Obviousness for the Claimed Embodiments of the Present Invention.**

The Examiner states that, "[t]he Examiner is using only the knowledge of the combinations of the references cited"<sup>9</sup> to support the pending rejections under 35 U.S.C. 103(a). However, as the Applicants note above, this very same art is either silent on or teaches away from the use of at least one element recited within the pending method claims. If the cited art fails to provide the knowledge required to recapitulate the invention as claimed, the Applicants respectfully submit the Examiner is using the knowledge provided by the Applicants'

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<sup>8</sup> Office Action mailed May 20, 2005, page 5.

<sup>9</sup> Office Action mailed May 20, 2005, page 7.

specification to render obvious the claims of the same. This is error. The Examiner is reminded that,

"[t]o imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher." *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 220 USPQ 303, 312-13 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)

Moreover, "the mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification." *In re Fritch*, 972 F.2d 1260, 1266, 23 USPQ 2d 1780, 1783-84 (Fed. Cir. 1992). Given the particularity with which the Applicants have documented: i) the elements of the claimed embodiments of the present invention not found in the cited art, ii) the failure of this same art to suggest a combination or modification which would recapitulate the invention as claimed, and iii) selected instances where this same art teaches away from the claimed embodiment of the present invention; the Applicants respectfully request the pending rejections be withdrawn and the claims passed to allowance.

### CONCLUSION

Should the Examiner believe a telephone interview would aid in the prosecution of this application, the Applicants encourage the Examiner to call the undersigned collect.

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Thomas W. Brown  
Registration No. 50,002

MEDLEN & CARROLL, LLP  
101 Howard Street, Suite 350  
San Francisco, California 94105  
617.984.0616